Early infantile epileptic encephalopathy 1

Early infantile epileptic encephalopathy 1 (EIEE1) is a seizure disorder characterized by a type of seizure known as infantile spasms. The spasms usually appear before the age of 1. Several types of spasms have been described, but the most commonly reported type involves bending at the waist and neck and extending the arms and legs (sometimes called a jackknife spasm). Each spasm lasts only seconds, but they occur in clusters several minutes long. Although individuals do not usually have spasms while they are sleeping, the spasms commonly occur just after awakening. Infantile spasms usually stop by age 5, but many children then develop other types of seizures that recur throughout their lives.

Most babies with EIEE1 have characteristic results on an electroencephalogram (EEG), a test used to measure the electrical activity of the brain. The EEG of these individuals typically shows an irregular pattern known as hypsarrhythmia, and this finding can help differentiate infantile spasms from other types of seizures.

Because of the recurrent seizures, babies with EIEE1 stop developing normally and begin to lose skills they have acquired (developmental regression), such as sitting, rolling over, and babbling. Most affected individuals also have intellectual disability throughout their lives.

Frequency

Infantile spasms are estimated to affect 1 to 1.6 in 100,000 individuals. This estimate includes EIEE1 as well as infantile spasms that have other causes.

Causes

EIEE1 is caused by mutations in the *ARX* gene. The protein produced from this gene plays a role in the normal functioning of the brain by regulating other genes that contribute to brain development. Research suggests that mutations in the *ARX* gene reduce the amount or function of the ARX protein. A shortage of ARX function is thought to disrupt normal brain development, leading to seizures and intellectual disability.

It is likely that mutations in other genes that have not been identified cause rare cases of EIEE1. Infantile spasms can also have nongenetic causes, such as brain malformations, other disorders that affect brain function, or brain damage. In addition, changes in genes that are not located on the X chromosome cause infantile spasms in rare cases.

Inheritance Pattern

EIEE1 is inherited in an X-linked recessive pattern. The *ARX* gene is located on the X chromosome, which is one of the two sex chromosomes. In males (who have only one X chromosome), one altered copy of the gene in each cell is sufficient to cause the condition. In females (who have two X chromosomes), a mutation would usually have to occur in both copies of the gene to cause the disorder. However, in some instances, one altered copy of the *ARX* gene is sufficient because the X chromosome with the normal copy of the *ARX* gene is turned off through a process called X-inactivation. Early in embryonic development in females, one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). X-inactivation ensures that females, like males, have only one active copy of the X chromosome in each body cell.

Usually X-inactivation occurs randomly, such that each X chromosome is active in about half of the body cells. Sometimes X-inactivation is not random, and one X chromosome is active in more than half of cells. When X-inactivation does not occur randomly, it is called skewed X-inactivation. Some *ARX* gene mutations may be associated with skewed X-inactivation, which results in the inactivation of the X chromosome with the normal copy of the *ARX* gene in most cells of the body. This skewed X-inactivation causes the chromosome with the mutated *ARX* gene to be expressed in more than half of cells, causing EIEE1.

A characteristic of X-linked inheritance is that fathers cannot pass X-linked traits to their sons.

Other Names for This Condition

- early infantile epileptic encephalopathy-1
- EIEE1
- epileptic encephalopathy, early infantile, 1
- infantile epileptic-dyskinetic encephalopathy
- ISSX
- ISSX1
- X-linked infantile spasm syndrome
- X-linked infantile spasm syndrome 1
- X-linked Ohtahara syndrome
- X-linked West syndrome

Diagnosis & Management

Genetic Testing Information

- What is genetic testing?
  /primer/testing/genetictesting
- Genetic Testing Registry: Epileptic encephalopathy, early infantile, 1
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C3463992/
- Genetic Testing Registry: West syndrome
  https://www.ncbi.nlm.nih.gov/gtr/conditions/C0037769/

Research Studies from ClinicalTrials.gov

- ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22X-linked+infantile+spasm+syndrome%22

Other Diagnosis and Management Resources

- Child Neurology Foundation
  https://www.childneurologyfoundation.org/disorder/infantile-spasms/
- National Organization for Rare Disorders (NORD) Physician Guide
  https://rarediseases.org/physician-guide/infantile-spasms/

Additional Information & Resources

Health Information from MedlinePlus

- Health Topic: Developmental Disabilities
  https://medlineplus.gov/developmentaldisabilities.html
- Health Topic: Epilepsy
  https://medlineplus.gov/epilepsy.html

Genetic and Rare Diseases Information Center

- West syndrome
  https://rarediseases.info.nih.gov/diseases/7887/west-syndrome

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Infantile Spasms Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Infantile-Spasms-Information-Page

Educational Resources

- Centers for Disease Control and Prevention: Intellectual Disability Fact Sheet
  https://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/IntellectualDisability.pdf
- MalaCards: epileptic encephalopathy, early infantile, 1
  https://www.malacards.org/card/epileptic_encephalopathy_early_infantile_1
- Orphanet: West syndrome
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=3451

Patient Support and Advocacy Resources

- Child Neurology Foundation
  https://www.childneurologyfoundation.org/disorder/infantile-spasms/
- Citizens United for Research in Epilepsy (CURE)
  https://www.cureepilepsy.org/
- National Organization for Rare Disorders (NORD): West Syndrome
  https://rarediseases.org/rare-diseases/west-syndrome/
- University of Kansas Medical Center Resource List: Developmental Delay
  http://www.kumc.edu/gec/support/devdelay.html

Scientific Articles on PubMed

- PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28x-linked+infantile+spasm+syndrome%5BTIAB%5D%29+OR+%28early+infantile+epileptic+encephalopathy%5BTIAB%5D%29+OR+%28infantile+epileptic-dyskinetic+encephalopathy%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+2520+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM

- EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 1
  http://omim.org/entry/308350

Medical Genetics Database from MedGen

- Epileptic encephalopathy, early infantile, 1
  https://www.ncbi.nlm.nih.gov/medgen/483052

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